1. SCIENTIFIC ABSTRACT

The proposed study is a Phase 1 trial to evaluate a HIV based lentiviral vector carrying an antisense sequence targeted to HIV in the treatment of HIV infection. The primary objective of this Phase I study is to determine the safety and tolerability of treatment with autologous CD4+ T cells modified (transduced) ex vivo with VRX496 when administered to HIV infected patients.

VRX496 is a completely gutted lentiviral vector and does not code for any viral proteins. The viral vector contains an antisense sequence targeted to the HIV envelope (env) gene. VRX496 directly interferes with wild-type HIV (wt-HIV) expression via anti-env antisense expression in vector transduced CD4 cells that become infected with wt-HIV. Expression of the anti-HIV antisense env from a HIV vector transcript would target wt-HIV RNA and destroy it, and hence, decrease productive HIV replication from CD4 T cells. The clinical goal for this treatment approach is to decrease viral loads and promote CD4 T cell survival in vivo.

Data from in vitro studies suggest that HIV vectors such as VRX496 could potentially reduce viral loads in HIV-infected individuals and thus could delay the onset to AIDS while promoting CD4 T cell survival and providing the immune system with a better chance to control the infection. Additionally, preliminary results from experiments in SCID mice (mice with transplanted human immune cells) indicate that the human cells transduced with VRX496 and implanted into the SCID mice do not elicit any overt adverse effects.

HIV-infected patients (CD4 T cell count of >200/mm^3, discontinued from HAART therapy) will undergo leukoapheresis with subsequent CD4 T cell isolation. Patient CD4 T cells will be transduced ex vivo with the vector, expanded for 8-11 days, and then the modified cells will be reintroduced into the patient. Each subject will receive a single intravenous injection infused over 30 minutes; subjects will be examined 24, 48, and 72 hours post-injection and weekly for 4 weeks. Patients will receive one of four different ascending doses (1×10^9, 3×10^9, 1×10^{10}, and 3×10^{10} cells/patient). Doses will be administered to four independent, sequential subject cohorts of 3 patients. Groups will be administered escalating doses at 6-week intervals after safety has been demonstrated in the previous group. Follow-up examinations will be

conducted 1, 3, and 6 months post-injection. Long term follow-up including RCR testing will be performed.